Modelling the elimination of river blindness using long-term epidemiological and programmatic data from Mali and Senegal

Martin Walker, Wima A Stolk, Matthew A. Dixon, Christian Bottomley, Lamine Diawara, Mamadou O Traoré, Sake J de Vlas, María-Gloria Basáñez

Supplementary information

1. Methods

1.1 EPIONCHO

1.1.1 Parasite life stages within human hosts

We begin our formal description of the refined version of EPIONCHO by reintroducing notation used in previous descriptions (Turner et al., 2013 and Basáñez et al., 2016). We use subscripts *s*, *d* and *j* to denote human sex, treatment adherence *and* exposure *to* ivermectin treatment. According to this notation, $X_{s,d,j}$ represents X in subgroup *s,d,j*, $X_{s,d}$ represents X in subgroup *s,d* (i.e., X is averaged over subgroup *j*) and X represents X averaged across the whole population. The treatment exposure structure indicated by *j* is required to capture the cumulative antifertility effects of ivermectin, tracking sub-populations exposed to different numbers of treatments. Although the model allows for differences between men and women, the results presented in this paper are based on a model that ignores sex-specific, differential exposure to blackfly bites.

A full list of model parameter together with function definitions are given in Table S1a – S1e for reference with the following mathematical description. We start by defining a partial differential equation for the number of immature L4 larval *Onchocerca volvulus* (infective L3 larvae inoculated with vector bites moult into L4 larvae, Duke, 1991), $L4_{s,d,j}(t,a)$ in hosts of age *a,* sex *s,* adherence group *d* and ivermectin exposure group *j*,

$$\frac{\partial L4_{s,d,j}(t,a)}{\partial t}+\frac{\partial L4_{s,d,j}(t,a)}{\partial a}=\Lambda_{s,d,j}(t,a)-\frac{1}{p}L4_{s,d,j}(t,a) \quad (1)$$

Here, the function $\Lambda_{s,d,j}(t,a)$ defines the incidence of new female larvae 'born' into exposure group *j* such that $\Lambda_{s,d,j}(t,a)$ either takes the value of the age- and sex-dependent force of infection from blackflies to humans, $\Delta H_s(t,a) = 0.5\beta(V/H)\Omega_s(a)\Pi_H[L3(t)]$, or 0 depending on time *t* and the number and frequency of ivermectin treatments being modelled (full details of this construction can be found elsewhere; Turner et al., 2013 and Basáñez et al., 2016). The force of infection includes terms V/H the vector to human ratio; β, the biting rate per blackfly on humans ($\beta(V/H)$ is the annual biting rate, ABR); $\Omega_s(a)$, the normalized age and sex-dependent vector exposure function (Filipe et al., 2005) and $\Pi_H[L3(t,a)]$, a density-dependent probability that incoming L3 larvae successfully establish as patent infections (Basáñez and Boussinesq 1999 and Basáñez et al., 2002). We do not consider explicitly the mortality of L4 larvae, but rather consider it implicitly as a reduction in the number of incoming larvae that successfully establish as adult parasites after a prepatent period *p*. The 0.5 constant in $\Delta H_s(t,a)$ captures that half of incoming L3 larvae are assumed to be female for a balanced sex ratio (Schulz-Key and Karam, 1986).

State variables for mean numbers of non-fertile and fertile adult female worms per human host are denoted $N_{s,d,j,i}(t,a)$ and $F_{s,d,j,i}(t,a)$ respectively, where i (i = 1,…,m) corresponds to the ith age category for adult worms, and s,d,j represent subgroups of human hosts defined by sex, adherence and exposure to ivermectin, as defined previously. These variables are defined by the following system of partial differential equations,

$$\frac{\partial N_{s,d,j,1}(t,a)}{\partial t}+\frac{\partial N_{s,d,j,1}(t,a)}{\partial a}=\frac{1}{p}L4_{s,d,j}(t,a)-(\omega+\sigma_W)N_{s,d,j,1}(t,a)+\left[\lambda_0+\lambda_{1,d}(\tau)\right]F_{s,d,j,1}(t,a)$$

$$\frac{\partial N_{s,d,j,i}(t,a)}{\partial t}+\frac{\partial N_{s,d,j,i}(t,a)}{\partial a}=\sigma_W N_{s,d,j,i-1}(t,a)-(\omega+\sigma_W)N_{s,d,j,i}(t,a)+\left[\lambda_0+\lambda_{1,d}(\tau)\right]F_{s,d,j,i}(t,a) \text{ for } i=2,3,\ldots,m$$

$$\frac{\partial F_{s,d,j,1}(t,a)}{\partial t}+\frac{\partial F_{s,d,j,1}(t,a)}{\partial a}=\omega N_{s,d,j,i}(t,a)-\left[\lambda_0+\lambda_{1,d}(\tau)+\sigma_W\right]F_{s,d,j,1}(t,a)$$

$$\frac{\partial F_{s,d,j,i}(t,a)}{\partial t}+\frac{\partial F_{s,d,j,i}(t,a)}{\partial a}=\sigma_W F_{s,d,j,i-1}(t,a)-\left[\lambda_0+\lambda_{1,d}(\tau)+\sigma_W\right]F_{s,d,j,i}(t,a)+\omega N_{s,d,j,i}(t,a) \text{ for } i=2,3,\ldots,m \quad (2)$$

Here, $(1/p)L4_{s,d,j}(t,a)$ is the rate at which new female parasites establish as (initially) non-fertile adults; ω is the rate that non-fertile females become fertile and λ_0 is the rate that they revert back to being non-fertile (in reproductive cycles as described by Schulz-Key and Karam, 1986). The function $\lambda_{1,d}(\tau)$ is the excess rate at which fertile female worms become non-fertile due to the influence of ivermectin (capturing the so-called embryostatic effect; Basáñez et al., 2008). This rate wanes with time since the last treatment round with ivermectin τ (Table S1d) and hence it also varies among human hosts within different adherence groups (who receive treatment at different frequencies).

The per capita mortality rate of adult parasites in Eqn. (2) is given by $\sigma_W = m\sigma_{W0}$, where $1/\sigma_{W0}$ is the life-expectancy of adult parasites and m is the number of nominal parasite age compartments included in the model. This multi-compartment construction of adult parasite states ensures that the distribution of survival times is gamma with mean $1/\sigma_{W0}$ (the life expectancy) and variance $1/(m\sigma_{W0}^2)$. We set the number of compartments m by assuming a constant variance-mean ratio $1/(m\sigma_{W0}) = 0.5$. This condition approximates the survival times reported by Plaisier et al. (1991) with an average of between 9 and 11 years with 95% of worms having died by 12.5 to 15 years (Table S1e). For example, for an average survival time of 10 years, and assuming a constant variance-mean ratio of 0.5, we set m = 20, corresponding to 95% parasites having died by 14 years. Alternatively, for an average survival time of 9 years, we set m = 18, corresponding to 95% of parasites having died by 12.75 years.

We assume that the fecundity of (fertile) female worms is independent of their age and hence the rate of production of mf is defined in terms of the total number of fertile worms of any age, $F_{s,d,j}(t,a) = \Sigma_i F_{s,d,j,i}(t,a)$. Similarly, we consider the mating probability, $\Phi[W_{s,d,j}(t,a), k_W]$, as a function of the mean number of female worms (invoking the usual assumption of an identical distribution of male worms among the human population; May, 1977) and hence we introduce the derived quantity $W_{s,d,j}(t,a) = \Sigma_i F_{s,d,j,i}(t,a) + \Sigma_i N_{s,d,j,i}(t,a)$. The mean number of mf per human host is defined by the following partial differential equation,

$$\frac{\partial M_{s,d,j}(t,a)}{\partial t}+\frac{\partial M_{s,d,j}(t,a)}{\partial a}=\Phi[W_{s,d,j}(t,a), k_W]\varepsilon^*\psi_{d,j}(t)F_{s,d,j}(t,a)-\left[\sigma_{M0}+\sigma_{M1,d}(\tau)\right]M_{s,d,j}(t,a) \quad (3)$$

where ε^* is the rate of microfilarial production per fertile female parasite, parameter σ_{M0} is the per capita mortality rate of mf and the functions $\psi_{d,j}(t)$ and $\sigma_{M1,d}(\tau)$ define, respectively, the cumulative reduction in the production of mf with increasing exposures to ivermectin (increasing j; Turner et al., 2013) and the mortality rate of mf following treatment (Basáñez et al., 2008; Table S1d). The net mean number of mf in a human host is given by summing over the number of treatment exposure groups, $M_{s,d}(t,a) = \Sigma_j M_{s,d,j}(t,a)$.

1.1.2 Parasite life stages within blackfly vectors

The life expectancy of *O. volvulus* larvae within blackflies is short relative to that of the other parasite life stages and we therefore assume that the mean numbers of L1, L2 and L3 larvae per blackfly are at equilibrium such that,

$$L1_{s,d}(t,a)=\frac{\Delta V_s(t,a)}{\mu_V+\alpha_V M_{s,d}(t,a)+\mu_H+v_1+\alpha_s}$$

$$L2_{s,d}(t,a)=\frac{v_1 L1_{s,d}(t,a)}{(\mu_V+v_2)}$$

$$L3_{s,d}(t,a)=\frac{v_2 L2_{s,d}(t,a)}{(a_H/g+\mu_V+\sigma_L)} \quad (4)$$

Here, the function $\Delta V_s(t,a) = \beta\Omega_s(a)\Pi_V[M_s(t,a)]$, is the force of infection from humans to blackflies resulting from bites taken on human hosts of age a, sex s and adherence group d, where $\Pi_V[M_s(t,a)]$ is a density-dependent probability that incoming mf successfully establish within the blackfly thoracic muscles and develop to the infective L3 stage (Basáñez and Boussinesq 1999 and Basáñez et al., 2002). Other parameters in Eqn. (4) are defined as follows: μ_V is the background per capita mortality rate of (uninfected) blackfly vectors; α_V is the excess per capita blackfly mortality rate associated within ingestion of mf; μ_H is the per capita mortality rate of humans hosts; v_1 and v_2 are per capita rates of progression from L1 to L2 and from L2 to L3 larvae respectively; α_s is the rate of change in exposure to blackly vectors with age among hosts of sex s; a_H is the proportion of L3 larvae shed per bite; g is the length of the gonotrophic cycle (here the average duration of the period between two consecutive bloodmeals assuming one bloodmeal per batch of blackfly eggs) and σ_L is the per capita mortality rate of L3 larvae (Table S1e).

An expression for $L3(t)$, the mean number of larvae being inoculated into humans at any time, which forms part of the force of infection from vectors to humans in (1) (and thereby couples the larval population dynamics within the blackfly vector to the human host worm life stages) is given by taking the expectation of $L3_{s,d}(t,a)\Omega_s(a)$ with respect to human host age, adherence group and sex,

$$L3(t)=\sum_d \rho_d \sum_s \rho_s \int_a L3_{s,d}(t,a)\Omega_s(a)\rho(a)\ \mathrm{d}a$$

Here ρ_d is the proportion of human hosts in adherence category d; ρ_s is the proportion of hosts of sex s and $\rho(a)$ is the proportion of hosts of age a. Hence, the terms ρ_s and $\rho(a)$ define the demographic structure of the human population. Taking expectations over the human host demography is also used to yield population averages for $N(t)$, $F(t)$ and $M(t)$, the latter being a principal output of EPIONCHO, the mean microfilarial intensity in the skin. Calculating average parasite intensities for demographic subgroups (e.g. in the over 5 year olds) is achieved in an analogous manner, averaging over the relevant (truncated) distribution of the host population.

1.1.3 Patterns of adherence to treatment with ivermectin

Treatment coverage, c, is the fraction of the total population that receives ivermectin. It is calculated as the sum of the fraction of the population treated every round $\rho_{d=1}$ and the fraction treated every other round, $\rho_{d=2}$ (with equal proportions treated at each round). The whole population comprises these fractions in addition to those systematically non-adherent with treatment, $\rho_{d=3}$ and those aged < 5 years who are ineligible for treatment, $1 - \int^{a=5}\rho(a)\ da$. Hence we can write a pair of equations to calculate $\rho_{d=1}$ and $\rho_{d=2}$ (two unknowns) given values of c and $\rho_{d=3}$ (and $\int^{a=5}\rho(a)\ \mathrm{d}a$),

$$c=\rho_{d=1}+\rho_{d=2}$$

$$1=\rho_{d=1}+2\rho_{d=2}+\rho_{d=3}+\int_{a=0}^{a=5}\rho(a)\,\mathrm{d}a \quad (6)$$

1.1.4 Prevalence of microfilaridermia

Previous versions of EPIONCHO have modelled the prevalence of skin microfilariae by assuming that a negative binomial distribution describes the number of mf per milligram of skin (Basáñez and Boussinesq 1999 and Basáñez et al., 2002). This approach, however, does not adequately reflect the rapid 'bounce back' in prevalence observed after treatment with ivermectin (particularly in hyperendemic settings; Alley et al., 1994) nor is it flexible enough to model repeated skin snips of variable weight. Here, we base our refined prevalence-intensity model on the approach of Bottomley et al. (2016) who considered the joint distribution of the number of microfilariae observed per skin snip and the underlying distribution of adult (fertile) female worms among hosts. Specifically, we assume that the number of mf per mg of skin, Y(t), follows a negative binomial distribution with overdispersion parameter k_M with mean at equilibrium, $f(X)=(\varepsilon^* wX)/\sigma_M$, where X is the *number* of adult female *O. volvulus* (at equilibrium), w is the weight of the skin snip, ε^* is the rate of microfilarial production per fertile female worm per mg of skin, and σ_M is the per capita mortality rate of mf. According to this model, the probability that an infected individual has a single positive skin snip is $1 - P(Y=0) = 1 - [1 + f(X)/k_M]^{-kM}$ and the probability that at least one is positive when n skin snips are taken is $1 - [1 + f(X)/k_M]^{-nkM}$.

We calculate the prevalence at time t by taking the expectation of $1 - [1 + f(X,t)/k_M]^{-nkM}$ with respect to the underlying distribution of adult female worms, which we assume follows a negative binomial distribution with mean $W_{s,d}(t,a) = N_{s,d}(t,a) + F_{s,d}(t,a)$ and overdispersion parameter k_W. Hence,

$$P_{s,d}(t,a)=1-\sum_X [1+f(X,t)/k_M]^{(-nk_M)} g[X|W_{s,d}(t,a)] \quad (7)$$

where $g()$ denotes the negative binomial probability mass function. The community-wide prevalence is given by taking expectations over the human host demography (age and sex) and treatment adherence structure.

1.2. ONCHOSIM

The ONCHOSIM simulations presented here were performed with ONCHOSIM version 2.58Ap9. The computer program has previously been made available, along with a formal mathematical description of the model, instructions on installing and running the model in Stolk et al. (2015). For the current analysis, most model-parameters were fixed at their previously published default values (Stolk et al., 2015). However, we modified the monthly biting rate to reflect the seasonality in transmission in the Bakoye and Gambia river basins. The relative biting rate was varied between simulations in order to simulate different pre-control endemicity levels (see section *1.4. Estimating community-specific biting rates*). For ease of reference, Table S2 provides a complete overview of all WORMSIM parameters and their assumed values for the current study. WORMSIM is a general modelling framework for helmintic infections that includes the ONCHOSIM model. Hence, certain parameters in Table S2 do not apply to onchocerciasis transmission but are listed anyway for the sake of completeness (indicated where applicable).

1.3. Parametric uncertainty

The parameters in EPIONCHO have all been either previously estimated (e.g. Basáñez and Boussinesq 1999, Basáñez et al., 2002 and Filipe et al., 2005) or inferred from the literature and expert opinion. This includes parameters pertaining to the refinements introduced here, such as, v_1 and v_2 that define rates of progression from L1 to L2 and from L2 to L3 larvae (Eqn. (4)) within the blackfly as well as estimates of the underlying overdispersion of adult parasites among human hosts (Bottomley et al., 2008) and mf among skin snips (Bottomley et al., 2016). EPIONCHO parameter values and their associated uncertainties (typically ranges, but sometimes credible

intervals) are given in Table S1c – S1e. We employ a sampling importance resampling (SIR) approach (Gambhir et al., 2015) to select parameter sets that are consistent with available data on coupled ABR and average community-wide microfilarial prevalence estimates from 9 communities in northern Cameroon (Basáñez and Boussinesq, 1999) where the ABR was measured as an average from multiple locations within and around each community in a savannah onchocerciasis setting (Renz and Wenk, 1987). We use these data to identify unique parameter sets and generate a plausible set of ABR-prevalence curves (Figure 2, main text).

The SIR approach combines information from the prior distribution (henceforth abbreviated to prior) of EPIONCHO parameters, $\boldsymbol{\theta}$ (Table S1a – S1e) and the likelihood of available data to resample parameter sets in a biased manner so that parameters achieving larger likelihoods are overrepresented compared to those associated with lower likelihoods. We define a uniform prior distribution for each parameter using the ranges listed in Table S1c – S1e and a binomial likelihood for the data on the number of microfilaria-positive individuals, $\boldsymbol{y}$, and a model-predicted endemic (mean) prevalence, P^*, that is given by the expectation of $P^*(a)$ with respect to human host age (note that we omit sex structure here and treatment adherence structure is not relevant in this pre-intervention context),

$$L\left(\mathbf{y} \mid \boldsymbol{\theta}, \mathbf{ABR}\right) = \prod_i h\left[y_i \mid P^*\left(\boldsymbol{\theta}, ABR_i\right)\right] \tag{8}$$

Here $h()$ denotes the binomial probability mass function and **ABR** is a vector of observed ABRs (corresponding to the number of observations in the savannah setting dataset, see below).

We embed a measurement error model within the SIR procedure to relate the *observed* ABRs (one paired with each observed prevalence π_i) to the *true* unobserved ABRs, integrating uncertainty in exposure to blackfly bites into the likelihood. Specifically, we assume that the observed ABR is Poisson distributed with mean corresponding to the *true* ABR. That is, we define $P(ABR_{obs}|ABR)$. However, the purpose of a measurement error model is to derive an expression for the distribution of the *true* quantity of interest (i.e. the *true* ABR, that initializes EPIONCHO) given the quantity *observed* with error. That is, we desire $P(ABR|ABR_{obs})$. This is found by applying Bayes' theorem,

$$P\left(ABR \mid ABR_{obs}\right) = \frac{P\left(ABR_{obs} \mid \mathrm{ABR}\right)P\left(ABR\right)}{\int_{ABR} P\left(ABR_{obs} \mid \mathrm{ABR}\right)P\left(ABR\right)\,dABR} \tag{9}$$

Here $P(ABR)$ represents the so-called *exposure* model (Carroll et al., 2006), the marginal distribution of *true* ABRs. This we define as a gamma distribution with shape and scale parameters a and b such that the denominator in Eqn. (9)—the marginal distribution of the *observed* ABRs—is a negative binomial distribution with mean ab and overdispersion parameter a. We estimated the parameters of this distribution using maximum likelihood techniques.

Equipped with the likelihood function of Eqn. 8 and the ABR measurement error model of Eqn. 9, we implemented the SIR algorithm as follows:

1. Sample 10,000 *true* ABR sets from $P(ABR|ABR_{obs})$, denoting set i, $\mathbf{ABR}^{(i)}$.
2. Sample 10,000 parameter sets from the prior, denoting set i, $\boldsymbol{\theta}^{(i)}$.
3. Run EPIONCHO and record the endemic prevalence $\mathbf{P}^{*(i)}$ for given $\mathbf{ABR}^{(i)}$ and $\boldsymbol{\theta}^{(i)}$.
4. Calculate the likelihood of the prevalence data $L^{(i)}$ given $\mathbf{P}^{*(i)}$.
5. Resample with replacement 500 sets from $\boldsymbol{\theta}^{(i)}$ with probability weights $L^{(i)}$.

1.4. Estimating community-specific biting rates

We ran multiple simulations for a range of ABRs concordant with the limits of the pre-intervention community microfilarial prevalence estimates in the River Bakoye (Mali) and River Gambia (Senegal) foci, between 23% and 85%. For each ABR we simulated the intervention (18 years of annual and 19 years of biannual MDA in the River Bakoye and the River Gambia foci respectively) using a fixed parameter set (Basáñez et al., 2016; Table S2) in ONCHOSIM (generating stochastic uncertainty) and different unique parameter sets in EPIONCHO (generating parametric uncertainty). We then filtered these simulations, selecting those that maximised the likelihood of the community-specific prevalence data. This was done for each stochastic run in ONCHOSIM—thereby retaining stochasticity in projections using the same ABR—and for each parameter set in EPIONCHO. We undertook this estimation approach in an iterative manner, using increasing incremental sequences of the longitudinal training datasets to estimate more accurately the underlying community ABR. The algorithm used to implement this approach is as follows (note that here and in section *1.5 Selecting maximum a posteriori (MAP) parameter sets*) n and m are here redefined from their previous use):

1. Choose $j = 1,2,...,n$ ABRs concordant with the range of prevalence estimates bounded by the extremes of the 95% credible intervals of the data.
2. Run $i = 1,2,...,m$ simulations of the intervention for each ABR_j and parameter set $\boldsymbol{\theta}^{(i)}$, where $\boldsymbol{\theta}^{(i)}$ is a unique parameter set in EPIONCHO (note that $m = 1$ for a single fixed set in ONCHOSIM).
3. Calculate the likelihood of a subset (used for training) of the sequence of microfilarial prevalence estimates $\boldsymbol{y}_k$ in each community for each of the $m \times n$ model projections, $L_{ijk} = p(\boldsymbol{y}_k|\boldsymbol{\theta}^{(i)}, ABR_j)$ (note that L_{ijk} is a stochastic quantity for ONCHOSIM).
4. Choose the ABR_j that maximises the likelihood of the data in each community, $L_{ik} = p(\boldsymbol{y}_k|\boldsymbol{\theta}^{(i)}, ABR_k)$ (note that this is done by maximising the mean of L_{ik} over stochastic simulations for ONCHOSIM).

1.5. Selecting maximum a posteriori (MAP) parameters sets

We calculated the community-specific contribution to the posterior probability of each EPIONCHO parameter set as the product of the likelihood of the community training dataset, $p(\boldsymbol{y}_k|\boldsymbol{\theta}^{(i)}, ABR_k)$ (using the maximum likelihood point estimate of the ABR), and the probability of the parameter set, $p(\boldsymbol{\theta}^{(i)})$, as calculated from the SIR procedure. We then summed these community contributions to calculate the (non-normalized) posterior probability. We defined the parameter set that maximised this quantity as the maximum a posteriori (MAP) set. The MAP sets were used for the point projections shown in Figure 3 of the main text and for the community-specific predictions of sustained elimination or resurgence. In ONCHOSIM, because we did not consider multiple parameter sets, we essentially assign $p(\boldsymbol{\theta}^{(1)}) = 1$ such that the posterior probability is defined solely by summed contributions to the likelihood of each community training dataset. We write the algorithm for selecting MAP parameter sets as follows:

1. Calculate community specific contributions to the posterior probability as $p(\boldsymbol{y}_k|\boldsymbol{\theta}^{(i)}, ABR_k) \times p(\boldsymbol{\theta}^{(i)})$ for $i = 1,2,...,m$ where $\boldsymbol{\theta}^{(i)}$ where $\boldsymbol{\theta}^{(i)}$ is a unique parameter set in EPIONCHO (note that $m = 1$ for a single fixed set in ONCHOSIM and $p(\boldsymbol{\theta}^{(1)}) = 1$).
2. Take the product of the community specific contributions to calculate the non-normalized posterior probability for each parameter set, $p(\boldsymbol{\theta}^{(i)}|\boldsymbol{y}, \boldsymbol{ABR}) = \prod_k p(\boldsymbol{y}_k|\boldsymbol{\theta}^{(i)}, ABR_k) \times p(\boldsymbol{\theta}^{(i)})$.
3. Select the MAP parameter set that achieves the highest value of $p(\boldsymbol{\theta}^{(i)}|\boldsymbol{y}, \boldsymbol{ABR})$.

1.6. Instructions for installing and running EPIONCHO

The new version of EPIONCHO used in this analysis is written in C++ code which is called from within R using the Rcpp package (Eddelbuettel, 2013). Please be aware that the code remains under development and is certainly not optimised for efficacy. It has also been largely developed and tested on Mac OS so there is no guarantee of smooth performance on a Windows platform. The first step to installing and running EPIONCHO is to create a new

working directory for R. In Windows this could be `C:/EPIONCHO` or in Mac OS `~/EPIONCHO`. Now place the EPIONCHO source code `EPIONCHOv2.cpp`, along with the R data file, `theta.Rdata`, into the newly created directory. These files are available online at http://dx.doi.org/10.1016/j.epidem.2017.02.005 in the file `EPIONCHO.zip`. The next step is to install the Rcpp package and load the library.

```
> setwd("~/EPIONCHO")
> install.packages("Rcpp")
> library("Rcpp")
```

To compile EPIONCHO and load the parameter values, use the `sourceCpp()` and `load()` functions.

```
> sourceCpp(file="EPIONCHOv2.cpp")
> load(file="theta.Rdata")
```

The compilation yields an R function with two arguments, `runEPIONCHO(theta,itervtn)`. The first argument, `theta`, is a list of parameter values and the second is a binary variable indicting whether the model should be run to endemic equilibrium only, `itervtn=0`, or whether an intervention should be simulated, `itervtn=1`. The intervention based on mass treatment with ivermectin is defined by the list elements within `theta` and is divided into 5 'blocks', each with a corresponding number of treatments, frequency of treatments and associated levels of coverage. For example, the default intervention defined by the values in list elements 4:18 show that 4 treatments for the first 4 blocks (`ntr1=4`, `ntr2=4`, `ntr3=4`, `ntr4=4`) are given at an annual frequency (`ftrt1=1`, `ftrt2=1`, `ftrt3=1`, `ftrt4=1`) and that no treatment is given in the final block (`ntr5=0`; the value of `ftrt5` is then ignored). Hence, in total, the intervention comprises 16 annual treatments (taking 16 simulated years to complete). The coverages associated with each block of treatments are given in the list elements `cov1=0.8`, `cov2=0.8`, `cov3=0.8`, `cov4=0.8`, `cov5=0.8`. Hence all 16 treatments are given at 80% coverage (with the final coverage value `cov5=0.8` ignored since it is associated with `ntr5=0`, i.e. zero treatments).

```
> cbind( (unlist( theta[4:18] )) )
      [,1]
ntrt1  4.0
ntrt2  4.0
ntrt3  4.0
ntrt4  4.0
ntrt5  0.0
ftrt1  1.0
ftrt2  1.0
ftrt3  1.0
ftrt4  1.0
ftrt5  1.0
cov1   0.8
cov2   0.8
cov3   0.8
cov4   0.8
cov5   0.8
```

Changing any of the list elements that define the number, frequency and coverage of treatment with ivermectin alters the modelled intervention. For example, the intervention implemented in the River Gambia focus, Senegal—which was initially based on annual treatments before switching to a biannual strategy (see Table S3) is defined

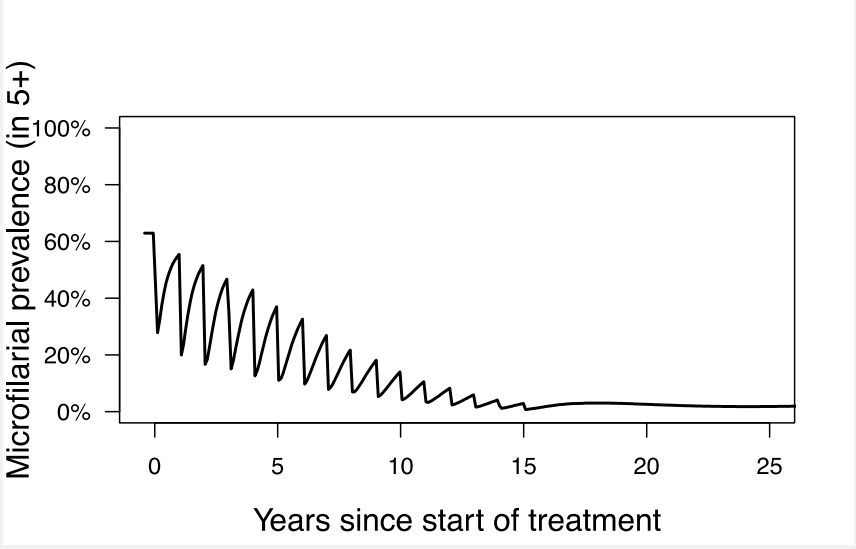
as follows: `ntr1=2; ntr2=4; ntr3=10; ntr4=2; ntr5=18` and `ftrt1=1; ftrt2=0.5; ftrt3=0.5; ftrt4=0.5; ftrt5=0.5`. The level of systematic non-adherence to treatment (the proportion of the population who are never treated) is defined by the list element `noncmp=0.05` (i.e., set to 5%). The list `theta` also includes elements `effVC` and `durVC` which relate to a vector control intervention, with `effVC` corresponding to the percentage reduction in the ABR caused by vector control and `durVC` the duration of implementation. We stress that vector control was not modelled in this analysis and the implementation is largely untested.

The majority of the other values contained within the list `theta` correspond to parameters that describe the various population processes modelled by EPIONCHO. Definitions are given in Tables S1a to S1e and the list element names are self-explanatory. The default values given for these parameters correspond to the MAP estimates for the model fitted to the complete longitudinal sequences of data from the River Bakoye, Mali and River Gambia, Senegal foci. Finally, `theta` also includes elements `nss` and `wtss` corresponding to the number of skin snips taken per person and the average weight of the skin biopsy. The default values are `nss=2` and `wtss=2`.

EPIONCHO is run by calling the `runEPIONCHO` function giving the arguments `theta` and `itervtn`. The model output comprises a list of 12 elements. These are: time in years since the start of the intervention (only negative values up to time 0 for `itervtn=0`), `time`; the mean number of L3 larvae per blackfly, `L3`; the mean number of mf per milligram of skin in the entire human population, `M`; the mean number of mf per mg of skin in individuals aged ≥ 5 years, `M5`; the mean number of mf per mg of skin in individuals aged ≥ 20 years, `M20`; the prevalence of mf recorded by `nss` skin snips of average weight `wtss`, `Mp`; the prevalence of mf in individuals aged ≥ 5 years, `Mp5`; the prevalence of mf in individuals aged ≥ 20 years, `Mp20`; the mean number of non-fertile adult female worms per person, `N`; the mean number of fertile female worms per person, `F`; the mean number of non-fertile or fertile female worms per person, `W` and the annual biting rate, `ABR` (which is returned from the imputed value contained within element `ABR` of `theta`).

```
> out <- runEPIONCHO(theta = as.double(theta), itervtn = 1)

> with(out, plot(I(Mp5*100)~time, type="l", yaxt="n", xaxt="n", ylim=c(0,100),
                  xlim=c(min(time), 25), lwd=2,
                        ylab="Microfilarial prevalence (in 5+)",
                              xlab="Years since start of treatment"))
> axis(2, at=c(0,20, 40, 60, 80, 100),
     labels =c("0%", "20%", "40%", "60%", "80%", "100%"), cex.axis=0.75, las=2)
> axis(1, at=c(0, 5, 10, 15, 20, 25), cex.axis=0.75)
```



2. Tables

Table S1a EPIONCHO parameter definitions, point estimates and prior ranges for West African savannah settings. *Human host demographic structure.*

Parameter / function	Definition	Point estimate (prior range)	Reference
$\rho(a) = \mu_H \exp(-\mu_H a)/[1 - \exp(-\mu_H a_{max})]$	truncated exponential distribution of proportion of human hosts of age a	NA	Filipe et al., 2005
a_{max}	maximum age of human hosts	80 years	Filipe et al., 2005
μ_H	human host population distribution inverse scale parameter	0.02 $year^{-1}$	Filipe et al., 2005

Table S1b EPIONCHO parameter definitions, point estimates and prior ranges for West African savanna settings. *Coverage and adherence to mass treatment.*

Parameter / function	Definition	Point estimate (prior range)	Reference
$\rho_F = \rho_M$	proportion of human women (set equal to ρ_M)	0.5	Filipe et al., 2005
$\rho_{d=1}$	proportion of human hosts eligible for treatment with ivermectin (aged ≥ 5 years) treated every round	Defined by therapeutic coverage and systematic non-adherence	
$\rho_{d=2}$	proportion of human hosts eligible for treatment with ivermectin (aged ≥ 5 years) treated every other round	Defined by therapeutic coverage and systematic non-adherence	
$\rho_{d=3}$	proportion of human hosts systematically non-adherent	0.05	

Table S1c EPIONCHO parameter definitions, point estimates and prior ranges for West African savannah settings. *Human host exposure to blackfly bites.*

Parameter / function	Definition	Point estimate (prior range)	Reference
$\Omega_s(a) = E_s\gamma_s E_0$ for $a < q$ $= E_s\gamma_s \exp[-\alpha_s(a - q)]$	age- and sex-specific exposure to biting blackfly vectors, including normalization constant γ_s	NA	Filipe et al., 2005
E_0	relative exposure to blackfly bites at birth relative to that at age q	0.1 (0.1, 0.1)	Filipe et al., 2005
$Q = E_M/E_F$	relative men to women exposure to biting blackfly vectors (here set to 1)	1.0 (1.0, 1.0)	
$\alpha_F=\alpha_M$	rate of change in exposure to blackly vectors with age among women (here set equal to α_M)	0.00 (-0.030, 0.012)†	Filipe et al., 2005
$\alpha_M=\alpha_F$	rate of change in exposure to blackly vectors with age among men (here set equal to α_F)	0.00 (-0.030, 0.012)†	Filipe et al., 2005
q	period of initial increase in exposure to vector bites during childhood	0.00 (0.00, 0.00)	Filipe et al., 2005

† range of sex-specific estimates from Filipe et al. (2005).

Table S1d EPIONCHO parameter definitions, point estimates and prior ranges for West African savannah settings. *Parasite and vector demographic rates.*

Parameter / function	Definition	Point estimate (prior range)	Reference
μ_V	per capita mortality rate of blackfly vectors	26 (12, 52)	Basáñez and Boussinesq, 1999
ε	per capita rate of microfilarial production per female adult parasite within human host	0.67 (0.54, 0.79)	Basáñez and Boussinesq, 1999
$\varepsilon^* = (\lambda_0+\sigma_{W0}+\omega)/\omega$	per capita rate of microfilarial production per fertile female adult parasite within human host	Defined by ε, λ_0, σ_{W0}, and ω	Basáñez et al., 2008
$\psi_{d,j}=1$ for $j=0$ $\psi_{d,j}=(1-\zeta)^{j-1}$ for $j>1$	modifying function of fertility of fertile female parasites exposed to j treatments	NA	Turner et al., 2013; Basáñez et al., 2016
ζ	cumulative reduction in female parasite fertility per exposure to treatment	0.35	Plaisier et al., 1995
$\sigma_W = m\sigma_{W0}$	per capita rate of progression of adult parasites through nominal age compartments	NA	
$1/\sigma_{W0}$	life-expectancy of adult parasites within human hosts	10 (9, 11)	Plaisier et al., 1991
$m = 2/\sigma_{W0}$	number of nominal age compartments of adult parasites you used m in the text; n better	Defined by σ_{W0}	Plaisier et al., 1991
σ_M	per capita mortality rate of mf within human hosts	0.8 (0.5, 3.0)	Basáñez and Boussinesq, 1999; Plaisier et al., 1995
σ_L	per capita mortality rate of L3 larvae within blackfly vectors	52 (26, 104)	Basáñez and Boussinesq, 1999
ω	per capita rate of progression from non-fertile to fertile adult parasites	0.59 (0.51, 0.68)	Basáñez et al., 2008
λ_0	per capita rate of reversion from fertile to non-fertile adult parasites	0.33 (0.23, 0.36)	Basáñez et al., 2008
$\lambda_{j1}(\tau) = \lambda_1^{max}\exp(-\varphi\tau)$	treatment induced per capita rate of reversion from fertile to non-fertile adult parasites at time τ since the last treatment	NA	
λ_1^{max}	maximum rate of treatment-induced sterility	32.4 (26.5, 40.9)	Basáñez et al., 2008
φ	rate of decay of treatment induced sterilisation	19.6 (15.9, 25.6)	Basáñez et al., 2008
$\sigma_{M1,d}(\tau) = (\tau + \upsilon)^{-\kappa}$	excess mortality rate of mf due to treatment	NA	Basáñez et al., 2008
υ	constant to allow for very large yet finite microfilaricidal effect at treatment	9.6×10^{-3} (1.2×10^{-3}, 20.5×10^{-3})	Basáñez et al., 2008
κ	shape parameter for excess mortality of mf following treatment	1.25 (1.12, 1.45)	Basáñez et al., 2008
v_1	per capita rate of progression from L1 to L2 larvae within blackfly vectors	73.14 (68.86, 77.76)†	Eichner et al., 1991
v_2	per capita rate of progression from L2 to L3 larvae within blackfly vector	133.57 (121.74, 147.41)†	Eichner et al., 1991

† refitted to data from Eichner et al. (1991). Rates are per year; durations are in years; proportions are dimensionless.

Table S1e EPIONCHO parameter definitions, point estimates and prior ranges for West African savannah settings. *Transmission rates and regulation of parasite population.*

Parameter / function	Definition	Point estimate (prior range)	Reference
ABR = $\beta V/H$ = $(V/H)(h/g)$	annual biting rate of blackfly vectors	Range calculated for each community	
V/H = ABR(g/h)	vector to host ratio	NA	Basáñez and Boussinesq, 1999
h	human blood index (fraction of blood meals taken on humans)	0.63 (0.58, 0.77)	Lamberton et al., 2016
$1/g$	reciprocal of the length of the gonotrophic cycle	104 (91, 122)	Basáñez and Boussinesq, 1999
a_H	proportion of L3 larvae shed per bite	0.8 (0.54, 1)	Basáñez and Boussinesq, 1999
$\Phi[W_{s,d,j}(t,a)] = 1+[1-W_{s,d,j}(t,a)/k_W]^{-(kW+1)}$	female worm mating probability	NA	May, 1977
k_W	overdispersion parameter of negative binomial distribution describing the distribution of adult parasites among human hosts	0.35 (0.31, 0.50)	Bottomley et al., 2016
k_M	overdispersion parameter of negative binomial distribution describing the distribution of mf in the skin of human hosts	0.26 (0.26, 0.70)	Bottomley et al., 2016
$\Pi_H[L3(t)] = [\delta_{H0} + \delta_{H\infty}c_H m\beta L3(t)] / [1 + c_H m\beta L3(t)]$	proportion of L3 larvae developing into adult worms within the human host, per bite	NA	Basáñez and Boussinesq, 1999; Basáñez et al., 2002
δ_{H0}	proportion of L3 larvae developing to the adult stage within the human host, per bite, when $m\beta L3(t) \rightarrow 0$	0.085 (0.038, 0.15)	Filipe et al., 2005; Basáñez et al., 2002
$\delta_{H\infty}$	proportion of L3 larvae developing to the adult stage within the human host, per bite, when $m\beta L3(t) \rightarrow \infty$	$2.9\text{x}10^{-3}$ ($8.5\text{x}10^{-4}$, $5.0\text{x}10^{-3}$)	Filipe et al., 2005; Basáñez et al., 2002
c_H	severity of density-dependent limitation of parasite establishment within humans	$5.9\text{x}10^{-3}$ ($1.8\text{x}10^{-3}$, $1.7\text{x}10^{-2}$)	Filipe et al., 2005; Basáñez et al., 2002
$\Pi_V[M_S(t,a)] = \delta_{V0}\exp[-c_V a_V M_S(t,a)]$†	proportion of mf per mg developing into infective larvae within the blackfly vector host per bite	NA	Churcher et al., 2006
δ_{V0}	proportion of mf per mg developing to the infective stage per bite when $M_S(t,a) \rightarrow 0$	0.014 (0.012, 0.017)‡	Soumbey-Alley et al., 2004
c_V	severity of density-dependent limitation of larval development per dermal microfilaria	0.0087 (0.0035, 0.017)‡	Soumbey-Alley et al., 2004
a_V	proportion of mf per mg of skin ingested per bite	0.4481 (0.3234, 0.6226)	Basáñez and Boussinesq, 1999
α_V	per capita excess rate mortality on blackfly vectors induced by mf	0.39 (0.25, 0.60)	Basáñez and Boussinesq, 1999

† derived in Churcher et al. (2006) for $k_W \rightarrow \infty$; ‡ refitted to data from Soumbey-Alley et al. (2004). Units as in Table S1d.

Table S2. WORMSIM quantification used to simulate onchocerciasis transmission.

Parameter	Value	Source
Human demography		
Cumulative survival F(*a*), by *age*		United Nations, 2013
0	1.000	
5	0.804	
10	0.772	
15	0.760	
20	0.740	
30	0.686	
50	0.509	
90	0.000	
Fertility rate per woman R(*a*)*, by age*		United Nations, 2013
0–14	0.000	
15–29	0.109	
30–49	0.300	
50+	0.000	
Population trimming	10% if population size exceeds 440.	Assumption
Transmission of infection		
General transmission parameters		
Relative biting rate (*rbr*)	Multiplied with the reference *mbr* values, to modify the monthly and annual biting rate: varied between simulations.	
Seasonal variation in contribution to reservoir (*mbr*)	Reference *mbr* values (Jan-Dec): Bakoye; 60, 0, 0, 0, 0, 116, 4065, 6008, 2934, 3150, 1236, 541 (ABR = 18110). Gambia: 1647, 775, 110, 0, 0, 1484, 4754, 4557, 2222, 1379, 1234, 1014 (ABR = 19176)	Entomological data collated by OCP
Transmission probability (*v*), i.e. the probability that an infective particle in the reservoir successfully develops into a parasite life stage that is capable of infecting a human host	*v* = 0.07345; see reference for the derivation of this value, given parameters for fly biology and development of infective L3 larvae within the fly.	Coffeng et al., 2014
Success ratio (*sr*)	*sr* = 0.0031	Plaisier, 1996; Duke, 1993

Parameter	Value	Source
Zoophily (*z, 1 -h*)	z = 0.04 ; h = 0.96	Habbema et al., 1996; expert opinion (OCP entomologists)
Individual relative exposure to flies		
Variation in by age and sex (*Exa*)	Zero at birth, linearly increasing between ages 0–20 from 0 to 1.0 for men and from 0 to 0.7 for women, and then constant from the age of 20 years onwards	Plaisier, 1996
Variation due to personal factors (fixed through life) given age and sex (α_{Exi})	Gamma distribution with mean 1.0 and shape and rate equal to 3.5	Plaisier, 1996; unpublished data from OCP
Individual relative contribution to infection in the fly population		
Variation by age and sex (*Coa*)	*Coa = Exa;* individual contribution and exposure to the cloud are perfectly correlated, given they are governed by the same fly bites.	Assumption
Variation due to personal factors (fixed through life) given age and sex (α_{Coi})	*Coi = Exi*; individual contribution and exposure to the cloud are perfectly correlated, given they are governed by the same fly bites.	Assumption
Host immunity to incoming infections		
Average impact of host immunity (α_{Imm})	Assumed irrelevant for onchocerciasis, hence α_{Imm} = 0; i.e. no effect of immunity on incoming infections.	Assumption
Immunological memory (β_{Imm})	Irrelevant given that α_{Imm} = 0.	Assumption
Life history and productivity of the parasite in the human host		
Average worm lifespan (*Tl*)	10 years	Plaisier et al., 1991
Variation in worm lifespan	Weibull distribution with shape 3.8.	Assumption; Plaisier et al., 1991
Prepatent period (*pp*)	1 year	Plaisier et al., 1991 which refers to Duke, 1980 and Prost, 1980
Age-dependent microfilaria production capacity, *R(a)*	*R(a)* = 1 for 0 ≤ *a* < 5 *R(a)* = 1-((a-5)/15) for 5 ≤ *a* < 20 *R(a)* = 0 for *a* > 20	Plaisier et al., 1991 which refers to Albeiz, 1985 and Karam et al., 1987
Longevity of microfilariae within host (*Tm*)	9 months	Plaisier, 1996
Mating cycle (*rc*)	3 months	Plaisier, 1996 which refers to Schulz-Key and Karam, 1986 and Schulz-Key, 1990
Male potential (*pot*)	100 female worms.	Plaisier, 1996

Parameter	Value	Source
Density-dependent female worm reproductive capacity		
Worm contribution to host load of infective material ($0(.)$)	7.6 mf/worm	Plaisier, 1996
Exponential saturation of individual female worm productivity per worm present in host (λ_z)	$\lambda_z = 0$ i.e. no exponential saturation.	Assumption
Morbidity		
Disease threshold (*Elc*) for blindness	Weibull distribution with mean 10.000 and shape 2.0	Coffeng et al., 2013
Reduction in remaining life expectancy due to blindness (*rl*)	50%	Coffeng et al., 2013 which refers to partly published data from OCP; Diadze et al., 1986; Plaisier et al., 1991. Diadze et al., 1986 and Plaisier et al., 1990 which refers to Prost and Vaugelade 1981 and Kirkwood et al., 1983
Infection dynamics in the cloud		
Cloud uptake of infectious material ($U(.)$)	Exponential saturating function with parameters a = 1.2, b = 0.0213, and c = 0.0861.	Plaisier et al., 1991 which refers to WHO, 1989 and Philippon, 1977.
Monthly cumulative survival of infective material in the central reservoir (ψ)	0%; i.e. the cloud represents a cloud of vectors that transmit infection within the same month.	Assumption
Mass treatment coverage		
Timing and coverage (C_w)	As reported for Bakoye and Gambia basins (see Table S3)	
Relative compliance ($c_r(k, s)$) *by age and sex*		Based on unpublished OCP data

age-group	cr(k,males)	cr(k,females)
0-4	0	0
5-9	0.75	0.5
10-14	0.8	0.7
15-19	0.8	0.74
20-29	0.7	0.65
30-49	0.75	0.7
50+	0.8	0.75

Parameter	Value	Source
Drug treatment		
Proportion of microfilariae cleared from host	100%	Plaisier et al., 1995
Duration of temporary reduction in female reproductive capacity (Tr_0), average	11 months	Plaisier et al., 1995
Permanent reduction in female worm reproductive capacity (d_0), average	34.9%	Plaisier et al., 1995
Proportion of adult worms killed (m_0)	0%	Plaisier et al., 1995
Relative effectiveness (v)	Weibull distribution with mean 1 and shape 2	Plaisier et al., 1995
Vector control		
Timing	Not used.	
Coverage	Not used.	
Surveys		
Timing	Surveys are done at yearly intervals from 1988-2021. They are always done in month 5, i.e. exactly 12 or 6 months after annual or biannual treatment respectively. The simulation allows for a 200-year warming-up period before the first survey in 1988.	
Dispersal factor for worm contribution to measured density of infective material (d)	Exponential distribution with mean 1	Plaisier et al., 1991
Variability in measured host load of infective material (eggs per gram faeces)	Poisson distribution with mean $ss(t)$	Plaisier et al., 1991

Table S3. EPIONCHO and ONCHOSIM assumptions on the timing of treatment and achieved coverage.

Gambia			**Bakoye**		
Year	**Month**	**Coverage**	**Year**	**Month**	**Coverage** †
1988	5	0.665	1989	5	0.605
1989	5	0.665			
1990	5	0.665	1990	5	0.605
1990	11	0.665			
1991	5	0.665	1991	5	0.605
1991	11	0.665			
1992	5	0.765	1992	5	0.765
1992	11	0.765			
1993	5	0.765	1993	5	0.765
1993	11	0.765			
1994	5	0.765	1994	5	0.765
1994	11	0.765			
1995	5	0.765	1995	5	0.765
1995	11	0.765			
1996	5	0.765	1996	5	0.765
1996	11	0.765			
1997	5	0.38	1997	5	0.38
1997	11	0.38			
1998	5	0.79	1998	5	0.78
1998	11	0.79			
1999	5	0.79	1999	5	0.78
1999	11	0.79			
2000	5	0.79	2000	5	0.78
2000	11	0.79			
2001	5	0.79	2001	5	0.78
2001	11	0.79			
2002	5	0.79	2002	5	0.78
2002	11	0.79			
2003	5	0.79	2003	5	0.78
2003	11	0.79			
2004	5	0.79	2004	5	0.78
2004	11	0.79			
2005	5	0.79	2005	5	0.78
2005	11	0.79			
2006	5	0.79	2006	5	0.78

† Assumptions regarding treatment adherence and malabsorption: 5% of individuals never takes treatment, e.g. because of refusal or serious illness (EPIONCHO, ONCHOSIM); 5% of the treatments is assumed to be ineffective, e.g. due to failure to swallow the drugs or malabsorption (ONCHOSIM only).

Table S4. Maximum likelihoods of the data in the River Bakoye focus, Mali and the River Gambia focus, Senegal given the estimated community-specific annual biting rates for EPIONCHO and ONCHOSIM.

Microfilarial prevalence training data	Maximum log-likelihood	
	EPIONCHO†	ONCHOSIM‡
Pre-intervention data only	-70.5	-109.2
Pre-intervention and next interim data points	-307.4	-462.2
Pre-intervention and next two interim data points	-445.2	-566.3
Complete longitudinal sequence	-672.3	-786.3

† corresponds to the maximised value for the maximum a posteriori parameter set (see *1.5. Selecting maximum a posteriori (MAP) parameters sets*); ‡ corresponds to the maximised mean value of the likelihood over stochastic simulations.

3. Figures

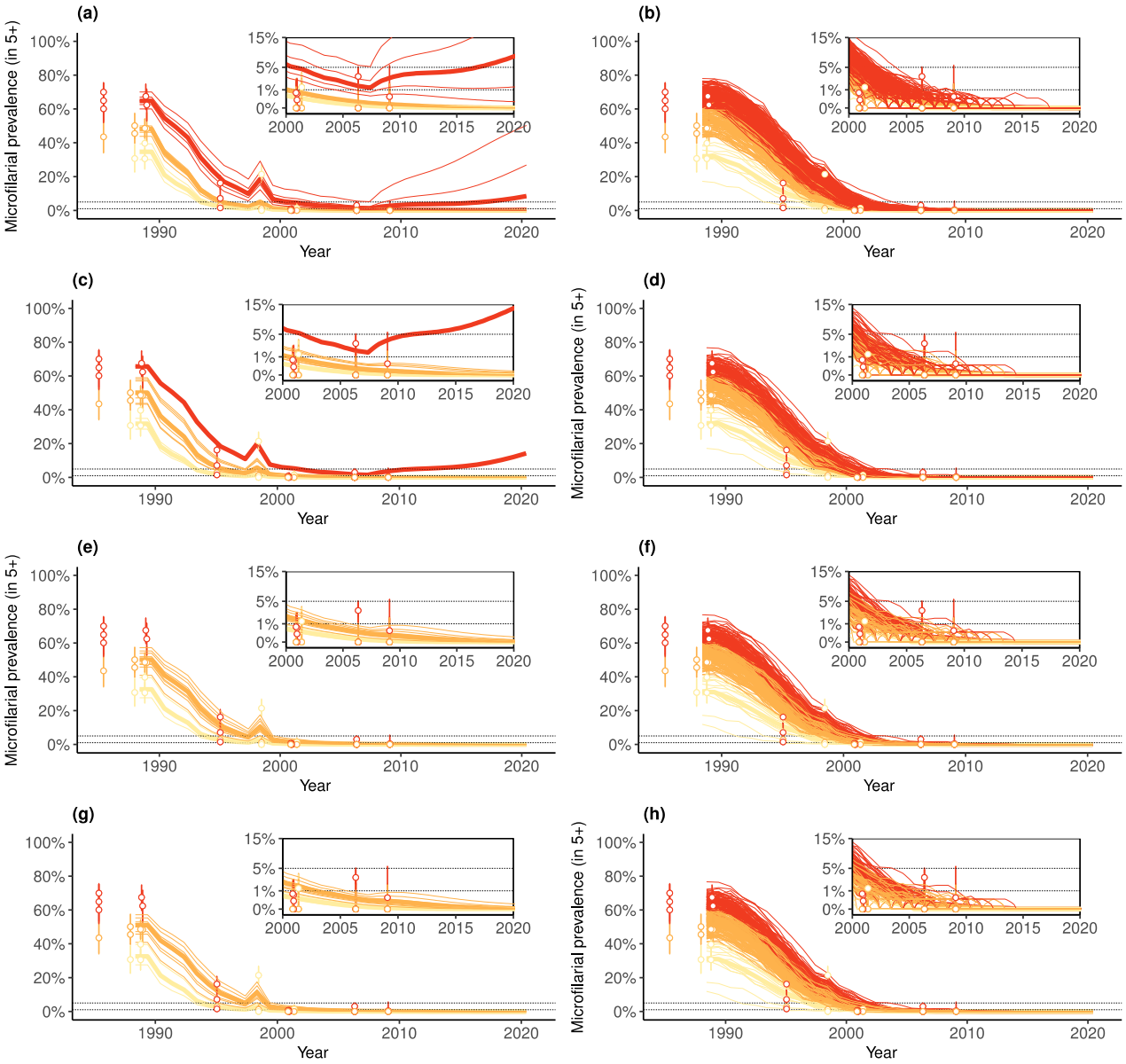


Figure S1. Observed and modelled dynamics of microfilarial prevalence in 13 communities from the River Bakoye focus, Mali. Panels on the left (a, c, e and g) and on the right (b, d, f and h) show EPIONCHO and ONCHOSIM projections, respectively. The thin lines correspond to community-specific simulations using maximum likelihood estimates of the community-specific annual biting rates (ABRs) and either the maximum a posterior (MAP) parameter set (EPIONCHO) or the default parameter set (ONCHOSIM). The estimated ABRs and MAP parameter sets are derived using the pre-intervention microfilarial prevalence data only (a, b); the pre-intervention data and the next interim data points (c, d); the pre-intervention data and the next two interim data points (e, f), and using the complete longitudinal sequence for each community (g, h). For ONCHOSIM there are many stochastic projections for each community projection; for EPIONCHO there is a single deterministic projection for each community, corresponding to the MAP parameter set. The thick solid lines show the median dynamics by endemicity category as categorised by a model-derived pre-intervention microfilarial prevalence in people ≥ 5 years of <40% (hypoendemic), 40%-59% (mesoendemic) and ≥60% (hyperendemic) and coloured sequentially from yellow to red. In panels e and g the estimated ABRs (from EPIONCHO) indicated all communities were either hypoendemic or mesoendemic. Panel insets show the period between 2010 and 2020 using a transformed *y*-axis for a better visual appraisal of the model projections compared to the data close to zero.

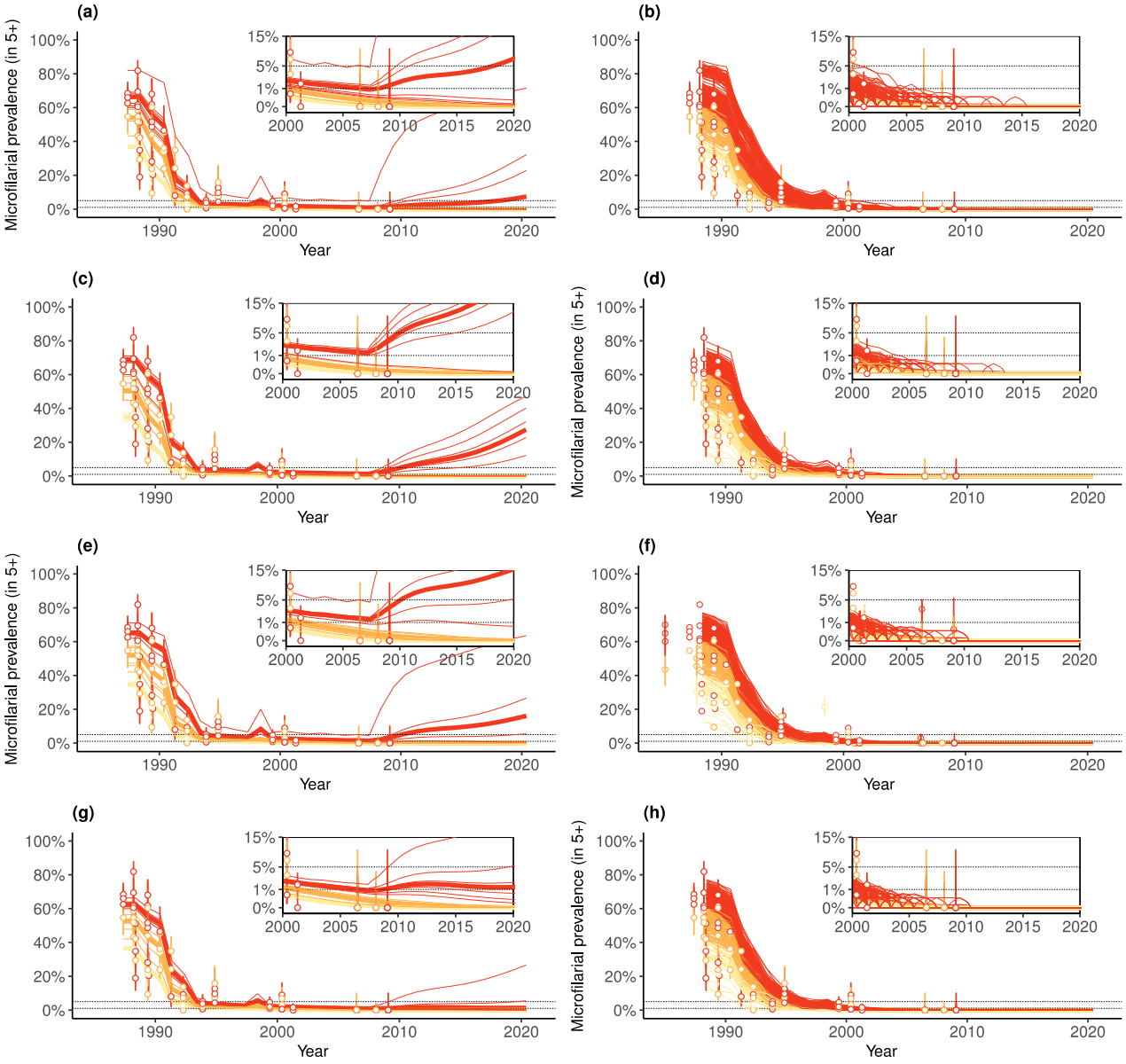


Figure S2. Observed and modelled dynamics of microfilarial prevalence in 14 communities from the River Gambia focus, Senegal. Panels on the left (a, c, e and g) and on the right (b, d, f and h) show EPIONCHO and ONCHOSIM projections, respectively. The thin lines correspond to community-specific simulations using maximum likelihood estimates of the community-specific annual biting rates (ABRs) and either the maximum a posterior (MAP) parameter set (EPIONCHO) or the default parameter set (ONCHOSIM). The estimated ABRs and MAP parameter sets are derived using the pre-intervention microfilarial prevalence data only (a, b); the pre-intervention data and the next interim data points (c, d); the pre-intervention data and the next two interim data points (e, f), and using the complete longitudinal sequence for each community (g, h). For ONCHOSIM there are many stochastic projections for each community projection; for EPIONCHO there is a single deterministic projection for each community, corresponding to the MAP parameter set. The thick solid lines show the median dynamics by endemicity category as categorised by a model-derived pre-intervention microfilarial prevalence in people ≥ 5 years of <40% (hypoendemic), 40%-59% (mesoendemic) and ≥60% (hyperendemic) and coloured sequentially from yellow to red. Panel insets show the period between 2010 and 2020 using a transformed *y*-axis for a better visual appraisal of the model projections compared to the data close to zero.

4. References

Albiez, E.J., 1985. Calcification in adult *Onchocerca volvulus*. *Trop. Med. Parasitol.* 36, 180-181.

Alley, E.S., Plaisier, A.P., Boatin, B.A., Dadzie, K.Y., Remme, J., Zerbo, G., Samba, E.M., 1994. The impact of five years of annual ivermectin treatment on skin microfilarial loads in the onchocerciasis focus of Asubende, Ghana. *Trans. R. Soc. Trop. Med. Hyg.* 88, 581-584. http://dx.doi.org/10.1016/0035-9203(94)90172-4.

Basáñez, M.G., Boussinesq, M., 1999. Population biology of human onchocerciasis. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 354, 809-826. http://dx.doi.org/10.1098/rstb.1999.0433.

Basáñez, M.G., Collins, R.C., Porter, C.H., Little, M.P., Brandling-Bennett, D., 2002. Transmission intensity and the patterns of *Onchocerca volvulus* infection in human communities. *Am. J. Trop. Med. Hyg.* 67, 669-679.

Basáñez, M.G., Pion, S.D.S., Boakes, E., Filipe, J.A.N., Churcher, T.S., Boussinesq, M., 2008. Effect of single dose ivermectin on *Onchocerca volvulus*: a systematic review and meta-analysis. *Lancet Infect. Dis.* 8, 310-22. d http://dx.doi.org/10.1016/S1473-3099(08)70099-9.

Basáñez, M.G., Walker, M., Turner, H.C., Coffeng, L.E., de Vlas, S.J., Stolk, W.A., 2016. River blindness: mathematical models for control and elimination. *Adv. Parasitol. Adv. Parasitol.* 94, 247-341. http://dx.doi.org/10.1016/bs.apar.2016.08.003.

Bottomley, C., Isham, V., Collins, R.C., Basáñez, M.G., 2008. Rates of microfilarial production by *Onchocerca volvulus* are not cumulatively reduced by multiple ivermectin treatments. *Parasitology* 135,1571-1581.

Bottomley, C., Isham, V., Vivas-Martinez, S., Kuesel, A.C., Attah, S.K., Opoku, N.O., Lustigman, S., Walker, M., Basáñez, M.G., 2016. Modelling Neglected Tropical Diseases diagnostics: the sensitivity of skin snips for *Onchocerca volvulus* in near elimination and surveillance settings. *Parasit. Vectors* 9, 343. http://dx.doi.org/10.1186/s13071-016-1605-3.

Carroll, R.J., Ruppert, D., Stefanski, L.A., Crainiceanu, C.M., 2006. *Measurement error in nonlinear models.* Chapman and Hall, London.

Churcher, T.S., Filipe, J.A.N., Basáñez, M.G., 2006. Density dependence and the control of helminth parasites. *J. Anim. Ecol.* **75**, 1313-1320. http://dx.doi.org/10.1111/j.1365-2656.2006.01154.x.

Coffeng, L.E., Stolk, W.A., Zouré, H.G.M., Veerman, J.L., Agblewonu, K.B., Murdoch, M.E., Noma, M., Fobi, G., Richardus, J.H., Bundy, D.A.P., Habbema, D., de Vlas, S.J., Amazigo, U.V., 2013. African Programme for Onchocerciasis Control 1995-2015: model-estimated health impact and cost. *PLoS Negl. Trop. Dis*. 7, e2032. http://dx.doi.org/10.1371/journal.pntd.0002032.

Coffeng, L.E., Stolk, W.A., Hoerauf, A., Habbema, D., Bakker, R., Hopkins, A.D., de Vlas, S.J., 2014. Elimination of African onchocerciasis: modelling the impact of increasing the frequency of ivermectin mass treatment. *PLoS ONE* 9, e115886. http://dx.doi.org/doi:10.1371/journal.pone.0115886.

Duke, B.O.L., 1980. Observations on *Onchocerca volvulus* in experimentally infected chimpanzees. *Tropenmed. Parasitol.* 31, 41–54.

Duke, B.O.L.,1991. Observations and reflections on the immature stages of *Onchocerca volvulus* in the human host. *Ann. Trop. Med. Parasitol*. 85, 103-110.

Duke, B.O.L., 1993. The population dynamics of *Onchocerca volvulus* in the human host. *Trop. Med. Parasitol.* 44**,** 61–68.

Eichner, M., Renz, A., Wahl, G., Enyong, P., 1991. Development of *Onchocerca volvulus* microfilariae injected into *Simulium* species from Cameroon. *Met. Vet. Entomol.* 5, 293-297. http://dx.doi.org/10.1111/j.1365-2915.1991.tb00555.x.

Filipe, J.A.N., Boussinesq, M., Renz, A., Collins, R.C., Vivas-Martinez, S., Grillet, M.E., Little, M.P., Basáñez, M.G., 2005. Human infection patterns and heterogeneous exposure in river blindness. *Proc. Natl. Acad. Sci. U S A*. 102, 15265-15270. http://dx.doi.org/10.1073/pnas.0502659102.

Gambhir, M., Singh, B.K., Michael, E., 2015. The Allee effect and elimination of neglected tropical diseases: a mathematical modelling study. *Adv. Parasitol.* 87, 1-31. http://dx.doi.org/10.1016/bs.apar.2014.12.001.

Habbema, J.D.F., van Oortmarssen, G.J., Plaisier, A.P., 1996. The ONCHOSIM model and its use in decision support for river blindness control. In Isham V, Medley G (Eds.), Models for infectious human diseases. Their structure and relation to data. Publications of the Newton Institute. Cambridge University Press, Cambridge, UK, pp. 360–380.

Karam, M., Schulz-Key, H., Remme, J., 1987. Population dynamics of *Onchocerca volvulus* after 7 to 8 years of vector control in West Africa. *Acta Trop*. 44, 445–457.

Kirkwood, B., Smith, P., Marshall, T., Prost, A., 1983. Relationships between mortality, visual acuity and microfilarial load in the area of the Onchocerciasis Control Programme. *Trans. R. Soc. Trop. Med. Hyg.* 77, 862–868.

Lamberton, P.H.L., Cheke, R.A., Walker, M., Winskill, P., Crainey, J.L., Boakye, D.A., Osei-Atweneboana, M.Y., Tirados, I., Wilson, M.D., Sampson, O., Post, R.J., Basáñez, M.G., 2016. Onchocerciasis transmission in Ghana: the human blood index of sibling species of the *Simulium damnosum* complex. *Parasit. Vectors* 9, 432. http://dx.doi.org/10.1186/s13071-016-1703-2.

May, R.M., 1977. Togetherness among schistosomes: its effects on the dynamics of the infection. *Math. Biosci.* 35, 301-343. http://dx.doi.org/10.1016/0025-5564(77)90030-X.

Philippon, B., 1977. Etude de la transmission d' *Onchocerca volvulus* (Leuckart, 1983) Nematoda, Onchocercidae) par *Simulium damnosum* (Theobald, 1903) (Diptera, Simuliidae) en Afrique tropicale. *Travaux et Documents ORSTOM*, 63.

Plaisier, A.P., van Oortmarssen, G.J., Habbema, J.D., Remme, J., Alley, E.S., 1990. ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. *Comput. Methods Programs Biomed.* 31, 43-56.

Plaisier, A.P., van Oortmarssen, G.J., Habbema, J.D., Remme, J., 1991. The reproductive lifespan of *Onchocerca volvulus* in West African savanna. 48, 271-284.

Plaisier, A.P., Soumbey-Alley, E., Boatin, B.A., van Oortmarssen, G.J., Remme, H., de Vlas, S.J., Bonneux, L., Habbema, D.F., 1995. Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the Onchocerciasis Control Programme in West Africa. *J. Infect. Dis.* 172, 204-210. http://dx.doi.org/10.1093/infdis/172.1.204.

Plaisier, A.P., 1996. Modelling onchocerciasis transmission and control. PhD thesis, Erasmus University, Rotterdam, The Netherlands. Available http://repub.eur.nl/pub/21404/.

Prost, A., 1980. Latence parasitaire dans l'oncbocereose. *Bull Wld. Hlth. Organ.* 58, 923-925.

Prost, A., Vaugelade, J., 1981. La surmortalité des aveugles en zone de savane ouest-africaine. *Bull. World Health Organ.* 59, 773-776.

Renz, A., Wenk, P., 1987. Studies on the dynamics of transmission of onchocerciasis in a Sudan-savanna area in North Cameroon V. What is a tolerable level of the annual transmission potential? *Annal. Trop. Med. Paraistol.* **81**, 263-274.

Schulz-Key, H., Karam, M., 1986. Periodic reproduction of *Onchocerca volvulus*. *Parasitol. Today* 2, 284–286.

Schulz-Key, H., 1990. Observations on the reproductive biology of *Onchocerca volvulus*. *Acta Leiden*. 59, 27–43.

Soumbey-Alley, E., Basáñez, M.G., Bissan, Y., Boatin, B.A., Remme, J.H.F., Nagelkerke, N.J.D., de Vlas, S.J., Borsboom, J.J.M., Habbema, D.F., 2004. Uptake of *Onchocerca volvulus* (Nematoda: Onchocercidae) by *Simulium* (Diptera: Simuliidae) is not strongly dependent on the density of skin microfilariae in the human host. *J. Med. Entomol.* 41, 83-94. http://dx.doi.org/10.1603/0022-2585-41.1.83.

Stolk, W.A., Walker, M., Coffeng, L.E., Basáñez, M.G., de Vlas, S.J., 2015. Required duration of mass ivermectin treatment for onchocerciasis elimimnation in Africa: a comparative modelling analysis. *Parasit. Vectors* 8: 552. http://dx.doi.org/10.1186/s13071-015-1159-9.

Turner, H.C., Churcher, T.S., Walker, M., Osei-Atweneboana, M.Y., Prichard, R.K., Basáñez, M.G., 2013. Uncertainty surrounding projections of the long-term impact of ivermectin treatment on human onchocerciasis. PLoS *Negl. Trop. Dis.* 7, e2169. http://dx.doi.org/10.1371/journal.pntd.0002169.

United Nations Department of Economic and Social Affairs Population Division, *World Population Prospects: the 2012 revision, Volume I: Comprehensive Tables*, 20